Notice to applicant

Central Administration of Pharmaceutical Products
General Administration For Stability

The General Administration of Stability FAQ
Year 2024

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The General Administration of Stability FAQ:

Administrative FAQ of the General Administration of Stability:

1. What is the implementation mechanism for submitting stability studies for pharmaceutical products under the Fast Track system?

In the first submission: The Fast Track system and payment codes for services are included in the same submission link without the need to submit a separate application or the presence of representatives of the applying companies to deliver applications or payment receipts, as companies can choose the (Fast Track) system

During the process: The companies can submit the Fast Track electronic request after submitting the stability study and during the review and evaluation process (process-in). The Companies can apply through the mechanism of unified link (electronic gate of General Administration of Stability) through this link: choose the General Administration of Stability Services then choose the Fast track request option to submit on Mondays each week:

https://forms.gle/dk1yp5BjtjKC9DqK8

While submitting the stability studies or appeals also the companies can apply for the following requests according to the published mechanisms:

a. Applying for Increasing the number of stability study files submitted above the permissible monthly limit for each company (One file per week)
b. Applying for Increasing the number of stability appeals submitted above the permissible monthly limit for each company (One file per week)

2. How can the company access the latest updates on submitting stability files to the General Administration of Stability?

By Browsing the Egyptian Drug Authority website and clicking on Laws, Decisions, and Regulations, then Announcements, then Service Recipient Notifications, then Central Administration of Pharmaceutical Products Notifications, and then General Administration of Stability Notifications.

3. What is the time for submitting a new stability study to be reviewed for locally and imported manufactured pharmaceutical products for the first time or fulfillment?

The mechanism for submitting stability studies has been updated so that it is in two stages only. During the first stage, the regulatory documents are reviewed, and the stability study file moves directly after that to the second stage, which is the Technical Evaluation, where the technical evaluation comments are sent in a grouped manner - if any-

• The number of stability studies allowed to be submitted will be according to the published submission guidance

• Submission link:

https://forms.gle/yVZCEUKWEvj1N7iu8

• Submission time:

On Tuesday and Wednesday of every week for all stability studies for local and imported products of all kinds

The company sends the required EDA Regulatory documents completions on Monday of every week for all stability studies for the various products on the link to the EDA Regulatory Documents.

https://forms.gle/x4zt445p7SkdPsn29

The company sends the required Technical Evaluation completions for all stability studies for various preparations on the Technical Evaluation completions link.

For local products:

https://forms.gle/a2iYJeE3ot9Nsnyq8

For imported Products:

https://forms.gle/33QLnPMmzGiX2ZVu7

4. In case of an inquiry, how can the company communicate it to the relevant administrations and units in the General Administration of Stability?

The General Administration of Stability allocated a window to receive inquiries from companies about the General Administration of Stability, weekly at the authority's headquarters in El Manial, Window No. 15.

10 am to 11 am concerning the Technical and Regulatory Administration

11 am to 12 pm concerning the Imported Examination Administration

12 am to 1 pm concerning the Local Examination Administration

In addition to the phone contact through the landline in the following appointments:

Follow-up unit (1302): 9 am to 3 pm all-day

Technical and Regulatory Administration (1301): 10 am to 12 pm

Local Examination Administration (1303): 10 am to 12 pm

Imported Examination Administration (1304): 10 am to 12 pm

With the continuation of receiving inquiries also the Companies can apply through the mechanism of unified link (electronic gate of General Administration of Stability) through this link: choose the General Administration of Stability Services then choose the Inquiries-complaints option to submit on Sundays and Wednesdays from 9:00 AM to 11:00 AM of each week:

https://forms.gle/dk1yp5BjtjKC9DqK8

Additionally, the companies can apply for a meeting with the administration's managers and the manager of General Administration of Stability to schedule the meetings on Mondays from 10 am to 3 pm.

.5. When can the concerned companies submit appeals regarding stability studies for local and imported products?

• Companies submit the complete appeal documents on Thursday of every week on the electronic submission link for appeals and pay the prescribed service fees.

• The General Administration of Stability conducts the technical evaluation and decides on the submitted appeal:

In case the submitted appeal is approved, the General Administration of Stability issues approval for the submitted appeal and sends an email to the company to receive the approval

In case the submitted appeal is not met, the General Administration of Stability will send a letter to the company with the required completion of the appeal.

The company submits appeal completions on Thursday of every week at the same link for electronic submission of appeals.

Note: Only allowed to submit one appeal weekly for each company otherwise apply for extra appeal according to the Fast Track mechanism.

Appeal link for local products:

https://forms.gle/sy1aXZ8zCz998snb6

Appeal link for Imported products:

https://forms.gle/YL6NDTmKRg4mp8bm6

6. How can the concerned companies track the status of a product after sending the Stability Tracking ID via email?

Please follow up on the status of the product on the electronic sheet using the code sent by email at the following link according to the product type and search the appropriate sub-sheet. The Companies can access through the mechanism of a unified link (electronic gate of General Administration of Stability) or on this link:

https://docs.google.com/spreadsheets/d/128qkyHnMqGFIMqQfgOFFLFIOZKcRf93xUEMIMNx5-Dw/edit?usp=sharing

7. What are the requirements for submitting a stability study for re-registration?

A long-term stability study or ongoing stability study is submitted to at least one production batch (if there is no change in the registered product data within the previous 10 years).

Please review the guidance of EDA Chairman decree 150/2022 for Reregistration requirements

https://www.edaegypt.gov.eg/media/3x4hcqc1/%D8%AF%D9%84%D9%8A%D9%84-%D8%AA%D9%86%D8%B8%D9%8A%D9%85%D9%8A_%D9%84%D9%82%D8%B1%D8%A7%D8%B1_%D8%B1%D9%8A-%D9%8A%D8%B3_%D8%A7%D9%84%D9%87%D9%8A%D9%8A-%D8%A9_150_%D9%84%D8%B3%D9%86%D8%A9_2022_hdr-recepf820-edaegy.pdf

8. What are the conditions that must be met when applying for an extension of the shelf life of pharmaceutical products?

Submit a long-term stability study on 3 production batches for the required shelf life otherwise the extrapolation could be applied according to ICH Q1E.

9. What is required to complete the registration procedures for an imported pharmaceutical product if accelerated and long-term stability studies on three production batches are unavailable?

The company submits an accelerated stability study and a long-term stability study on three primary batches of the product manufactured with the same composition statement and the proposed market packaging. The license holder company should commit to conducting an accelerated stability study and a long-term stability study on three production batches and submit them upon completion.

10. What is required to complete the registration procedures for an imported pharmaceutical product if a stability study on three production batches produced within the last ten years is unavailable?

An accelerated and long-term stability study can be submitted on the three production batches produced more than ten years ago, supported by an Ongoing stability study on a production batch produced within the previous ten years.

11. What are the studies and number of batches required for stability studies in the case of re-registration of an imported pharmaceutical product?

An Ongoing stability study is submitted on only one production batch. However, if the shelf life or storage conditions of the product are changed from those mentioned in the registration license, an Ongoing stability study is submitted on three production batches with the proposed shelf life under the proposed storage conditions.

12. What studies must be submitted for disinfectants in the case of re-registration, changes, and different packaging and sizes?

In the case of re-registration: A long-term stability study is submitted on only one production batch provided that no data about the previously registered product is changed.

In case of changes to registered pharmaceutical products: The required stability studies are submitted with the variation approval letter issued for the product.

In case of different sizes: The stability studies applied on each size should be submitted unless a Bracketing design is applied according to ICH Q1D For Bracketing and Matrixing is applied with justification.

13. Is there a list of Non-Reference Countries?

There is no list of non-reference countries. However, there is a list of reference countries approved by the Technical Committee on December 31, 2009, and the recent update on January 18, 2024. Countries not mentioned in this list are considered non-reference countries.

The list includes the following countries:

1. Australia- Austria- Belgium- Canada- Denmark- Germany- Finland- Iceland- France- Ireland- Luxembourg- Netherlands- New Zealand- Norway- Sweden- Switzerland- United States of America- United Kingdom- Japan- Italy- Spain- Portugal
2. WHO Listed Authorities
3. Operating as ML4 at benchmarked by WHO (Singapore & South Korea)

According to the published decisions:

https://edaegypt.gov.eg/media/0p5dtowr/reference-countries.pdf

https://edaegypt.gov.eg/media/55hgxep0/%D9%82%D8%B1%D8%A7%D8%B1-%D8%A7%D9%84%D9%84%D8%AC%D9%86%D8%A9-%D8%A7%D9%84%D9%81%D9%86%D9%8A%D8%A9-%D9%84%D9%85%D8%B1%D8%A7%D9%82%D8%A8%D8%A9-%D8%A7%D9%84%D8%A3%D8%AF%D9%88%D9%8A%D8%A9-%D9%81%D9%8A-18-1-2024-%D9%84%D9%84%D8%AF%D9%88%D9%84-%D8%A7%D9%84%D9%85%D8%B1%D8%AC%D8%B9%D9%8A%D8%A9_.pdf

14. What is required to reduce the shelf life of an imported pharmaceutical product?

For registered products: The General Administration responsible for the product is contacted to consider the request and get a variation approval.

For products under registration: The company submits the appeals link on Thursday of each week and uploads the required documents:

- A declaration letter from the License Holder requesting shelf-life reduction and stating the scientific justification for this reduction.

15. What is included in a stability study for local or imported pharmaceutical products to approve an In-use stability study?

An In-use stability study is submitted on at least two pilot batches, with at least one of the batches being selected close to the end of its shelf life. The study is conducted throughout the proposed in-use period at the initial and final time points.

16. How to fulfill a commitment in the stability approval?

An appeal must be submitted to the Appeals link on Thursday of each week

The administration will revise your appeal and respond with comments if any via email. An approval of fulfillment will be issued and received from the administrator on Tuesdays and Thursdays.

17. How to submit Imported stability studies that the company has undertaken to submit by a certain date and were required as a condition in the stability approval?

- Submit directly on Tuesday and Wednesday of every week according to the new submission guidance
- If the company exceeds the deadline specified in the stability approval for submitting the study, the company must first submit an appeal to obtain a payment receipt to obtain approval to extend the deadline for submitting the study. Then, submit the study.

17. How to modify or add any information in the stability approval, such as adding an after-opening study, adding a solvent, or modifying a drug specification?

• Companies submit appeal documents on Thursday of every week on the electronic submission link for appeals and pay the prescribed service fees.

• The General Administration of Stability conducts the technical evaluation and decides on the submitted appeal:

• In case the submitted appeal is approved, the General Administration of Stability issues approval for the submitted appeal and sends an email to the company to receive the approval

• In case the submitted appeal is not met, the General Administration of Stability will send a letter to the company with the required completion of the appeal.

19. What types of appeals can the companies submit?

1. Appeal (Technical) for Technical Evaluation comment replies
2. Approval letter adjustments such as adding an after-opening study, adding a solvent, or modifying a drug specification
3. Certain Cases Appeal (as in submission guidance)
4. Replacement for missed approval

Technical FAQ of the General Administration of Stability FAQ:

1. Is it acceptable to perform active ingredient analysis using an analytical method other than HPLC?

Yes, according to ICH Q6A, where the use of a nonspecific assay is justified, other supported analytical procedures should be used to achieve overall specificity for example where titration is adopted to assay a drug substance for release. The combination of the assay and a suitable test for impurities can be used.

2. Is a Photostability study submitted as part of the stability study for an imported pharmaceutical product?

Yes, according to TRS 986 annex 6. photostability should be an integral part of stress testing. The standard conditions are described in ICH Q1B. If “Protect from Light” is stated in one of the officially recognized pharmacopeia for the API. It is sufficient to state "Protect from Light" on labeling in lieu of photostability studies. When the container closure system is shown to be light protected when available It is acceptable to provide relevant data in the scientific literature (CMC/ public assessments reports) to support the idea of degradation products and pathways.

3. Are there any additional stability studies required for the registration or re-registration of an imported bulk/local bulk pharmaceutical product?

According to WHO TRS 1010 annex 10, Hold-time studies of bulk products, e.g. coated tablets prior to final packaging. For example, when the bulk product may be stored for a period exceeding 30 days before being packaged and/or shipped from a manufacturing site to a packaging site, the stability of the bulk product in the intended bulk container should be evaluated and studied. In the case of hold-time studies, Intermediates are stored. Further guidance can be found in the WHO TRS 992 annex 4. Where batches of finished products made from intermediates or bulk products subjected to a hold time study should be considered for long-term stability testing.

4. What are required documents and studies are required if there is a deviation (excursions) during the shipment of an imported pharmaceutical product and the product's approved storage conditions are deviated from?

Maintaining stability during the import of bulk drug products is crucial. However, unforeseen deviations from planned storage conditions (excursions) can occur during shipping. To ensure product quality and public safety, the importer must document the excursion details (type, duration), and assess its impact on stability considering product characteristics and severity of the deviation (reference: ICH Q1A(R2) Stability Testing of New Drug Substances and Products. Corrective actions might involve retesting the bulk product or extending the expiry date with scientific justification. Proper documentation of the excursion and the chosen course of action is essential for regulatory approval.

The following are submitted:

- An accelerated stability study of the product to evaluate the effect of the excursion that occurred during shipment and deviation from the approved product storage conditions and to ensure the stability of the product at the temperature mentioned for the period mentioned in the inspection report.
- The inspection report explaining the excursion and its transfer to the General Administration of Stability or an email from the Imported Medicines Inspection Department to the General Administration of Stability attached with the inspection report explaining the deviation.

5. What are the requirements if the stability method of analysis is by U.V., not HPLC?

If the stability method of analysis is by UV spectrophotometry instead of HPLC, the key requirements would be:

A. Wavelength Selection only in the maximum + or - 2 nm.

Select a wavelength where the analyte exhibits strong and specific absorbance of 220 -400 nm

B. Linearity in the range of beer's lumber law i.e choose concentrations that give absorbance 0.2 - less than 1 Au
C. Specificity under the selected wavelength ensures the analyte absorbance is not interfered with by excipients or potential degradation products
D. Robustness

- Assess the impact of small variations in parameters like pH, temperature, and sample prep on quantification

- Evaluate the method's ability to remain unaffected by minor changes

Note solvent change or pH change is critical and may alter wavelength (bathochromic or hypsochromic shift)

E. Stability-Indicating Capability

- Confirm method can accurately quantify analyte in the presence of degradation products

- May require comparison to reference HPLC method or other orthogonal techniques

F. Sample Preparation sample must be completely dissolved, if turbidity increases absorbance by false

NB details are found in USP < 857> Ultraviolet-Visible Spectroscopy

6. Is The forced degradation study required even if the stability study includes related substances according to the pharmacopeial monograph?

Performing related substance analysis according to the pharmacopeial monograph is essential for ensuring purity & Quality of FPP. However, this analysis alone does not replace the need for forced degradation studies which are crucial for several reasons.

a. They help in understanding the degradation pathways and intrinsic stability of the molecule
b. Regulatory requirements, as set required as part of the stability testing (stress testing), additional crucial information about stability through product degradation Behavioral predictions to ensure the safety and efficacy of the products

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7. Is the related substances test not required If the finished product is not pharmacopeia?

Related substance tests should be performed according to ICH guidelines Q3B

8. In the case of an in-use stability study, is it mandatory to perform a batch near the expiry date?

Yes, according to stability TRS 1010 Annexes, one batch at least should be submitted near the expiry date.

Questions adapted from FDA Q&A for stability

1. When do intermediate stability studies need to be initiated in the event of failure at accelerated conditions?

- An applicant should start accelerated, intermediate, and long-term stability studies simultaneously. This ensures data availability for submission if an accelerated stability study fails.

4. If one among the three batches in accelerated condition shows a significant change, what should be done?

If accelerated data show a significant change or failure of any attribute in one or more batches the applicant should submit:

- Submit intermediate data for all three batches.
- Include a failure analysis in the submission. (i.e., discussion concerning observed failures(s)).

3. How is the proposed shelf life supposed to be calculated? Will 6 months of accelerated data equal 24 months in the long term?

- ICH Q1E principles guide shelf-life calculation.
- Data from three ANDA submission batches (6 months), successful accelerated data (no significant change per ICH Q1A(R2)), and 12 months of stable long-term data (without variability) can support extrapolation to a 24-month shelf life without statistical evaluation, with appropriate post-approval stability commitments can be used to support extrapolation to a 24 months shelf life
- If accelerated data shows significant change, ICH Q1E Appendix A provides guidance on when intermediate condition stability data is recommended.

4. Can the Agency clarify expectations around the number of batches to support tests such as preservative effectiveness?

- One of the primary drug product batches should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life's end.
- The drug product specification should include a preservative content test, conducted in all stability studies.

Questions adapted from EMA Questions and answers on quality of herbal medicinal products/traditional herbal medicinal products - Scientific guideline

1. Is it possible to use skip testing for the microbiological quality of herbal medicinal products in specifications for stability studies performed under accelerated/intermediate conditions?

- No. Optimal growth temperatures for some microorganisms, especially human-pathogenic ones, are within the 30°C to 40°C range. These conditions, combined with high relative humidity (e.g., 75%), are ideal for microbial growth.
- Microbiological quality testing is essential for these studies, with compliance demonstrated at the beginning (batch release) and end of stability studies as a minimum requirement.

2. Is it possible to replace the testing of microbiological quality with the testing of the water activity (AW)?

- No. Microbiological quality testing is still mandatory at the beginning (batch release) and end of a stability study. Water activity (AW) testing can give additional information during the stability study but cannot replace it.

5. Are stability overages for herbal active substances acceptable?'

In general, as the whole herbal substance/preparation is considered as the active substance, stability overages would not be acceptable. However, stability overages would be acceptable for standardized extracts if justified.

References:

A. https://www.fda.gov/files/drugs/published/ANDAs--Stability-Testing-of-Drug-Substances-and-Products--Questions-and-Answers.pdf
B. http://academy.gmp-compliance.org/guidemgr/files/2010_EMA_HERBAL_Q_AS.PDF